

RECEIVED
CENTRAL FAX CENTER

10/697,473

OCT 31 2007

In the claims:

1. (Currently Amended) A chronotherapy tablet comprising: a [[cylindrical]] cylindrical core resulting from compression of granulations having a longitudinal axis, a first end and a second end, the core being comprised of at least two superposed layers of different compositions wherein an interface between each layer is substantially perpendicular to the longitudinal axis of the core and wherein at least one of the layers is a pharmacologically active composition; a compression coating which envelops the core, except for; at least one exposed release face of the core at at least one end of the core, wherein at least one exposed release face is substantially perpendicular to the longitudinal axis of the core; and, whereas upon oral administration the chronotherapy tablet effects the amelioration of at least one chronobiological condition within 24 hours.
2. (Currently Amended) A chronotherapy tablet according to claim 1 comprising two layers of pharmaceutical compositions separated by a layer of a different composition wherein the coating comprises water-soluble pore-forming material that [[substantially leaches out of the coat and thereby introduces mechanical instability]] form pores after a drug release period is substantially complete, wherein the coat remains intact throughout the release period but disintegrates prior to evacuation.
3. (Original) A chronotherapy tablet according to claim 1 comprising at least two layers of different pharmaceutical compositions.
4. (Original) A chronotherapy tablet according to claim 2 wherein two layers of different pharmaceutical compositions are separated by a layer of a different composition.
5. (Previously Presented) A chronotherapy tablet according to claim 3 wherein the coating envelops the core, except for two exposed release faces of the core wherein one release face is at the first end of the core and a second release face at the second end of the core.
6. (Original) A chronotherapy tablet according to claim 4 comprising three layers of three different pharmaceutical compositions.
7. (Original) A chronotherapy tablet according to claim 2 comprising two layers of the same pharmaceutical composition separated by a layer of a different composition.
8. (Original) A chronotherapy tablet according to claim 1 wherein at least one of the layers of compositions is a delay layer.
9. (Original) A chronotherapy tablet according to claim 3 wherein the first layer is a delay layer.
10. (Original) A chronotherapy tablet according to claim 4 wherein the layer of a different composition is a delay layer.
11. (Original) A chronotherapy tablet according to claim 7 wherein the layer of a different composition is a delay layer.

10/697,473

12. (Original) A chronotherapy tablet according to claim 2 comprising at least three layers of pharmaceutical compositions and two delay layers wherein the three layers of pharmaceutical compositions are each separated from each other by a delay layer.

13. (Previously Presented) A chronotherapy tablet according to claim 9 comprising a second layer adjacent to the first layer which second layer comprises a therapeutically effective amount of a drug, and a third layer adjacent to the second layer which third layer comprises a therapeutically effective amount of a drug, and wherein the delay layer provides for substantially complete dissolution of the delay layer between about 5 to about 9 hours after oral administration; and, the drug is selected from the group consisting essentially of a nonsteroidal anti-inflammatory agent, acetylsalicylic acid, sodium or potassium diclofenac, etodolac, indomethacin, ketorolac tromethamine, sulindac, tolmetin sodium, cyclooxygenase-2 inhibitor, celecoxib, rofecoxib, a fenamate, mefenamic acid, fluclofenac, an oxicam, meloxicam, piroxicam, piroxicam cyclodextrin, tenoxicam, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium, oxaprozin, and diflunisal.

14. (Original) A chronotherapy tablet according to claim 13 wherein the second layer comprises a therapeutically effective amount of naproxen and the third layer comprises a therapeutically effective amount of naproxen.

15. (Original) A chronotherapy tablet according to claim 14 wherein the second layer comprises between about 175 mg-675 mg naproxen wherein said naproxen is substantially completely releasable within about 15 minutes of substantially complete dissolution of the delay layer under physiological conditions; and, the third layer comprises between about 100 mg-250 mg naproxen that is releasable, after substantially complete dissolution of the second layer, at a substantially constant rate over a period of about 5 hours under physiological conditions.

16. (Original) A chronotherapy tablet according to claim 15 wherein the second layer comprises about 250 mg naproxen and the third layer comprises about 125 mg naproxen.

17. (Original) A chronotherapy tablet according to claim 12 wherein the first layer comprises a therapeutically effective amount of a drug, further comprising a second layer adjacent to the first layer which second layer is a delay layer, a third layer adjacent to the second layer which third layer comprises a therapeutically effective amount of a drug, a fourth layer adjacent to the third layer which fourth layer is a delay layer, a fifth layer adjacent to the fourth layer which fifth layer comprises a therapeutically effective amount of a drug, wherein the second and fourth delay layers each provide for substantially complete dissolution of the delay layer to require between about 5 to about 9 hours, each, during dissolution of the core under physiological conditions; and, the drug is selected from the group consisting essentially of an alpha-adrenergic blocking agent, doxazosine mesylate, prazosin hydrochloride, terazosine hydrochloride dehydrate, an Alpha & Beta-adrenergic blocking agent, labetalol hydrochloride, a Beta-adrenergic blocking agent, a selective non ISA, atenolol, bisoprolol, esmolol hydrochloride, metoprolol hydrate, a Beta adrenergic blocking agent, a non selective ISA, oxprinolol hydrochloride, pindolol, a Beta-adrenergic blocking agent, a non-selective non-ISA, nadolol,

10/697,473

propanolol hydrochloride, timolol maleate, a centrally acting antiadrenergic agent, clonidine hydrochloride, methyldopa, a Calcium Channel Blocker, amlodipine besylate, diltiazem hydrochloride, felodipine, nifedipine, verapamil Hydrochloride, a Vasolidator, diazoxide, epoprostenol sodium, hydralazine hydrochloride, minoxidil, a Potassium sparing agent, amiloride hydrochloride, spironolactone, triamterene, an Angiotensin converting enzyme inhibitor, benazipril hydrochloride, captopril, enalapril maleate, lisinopril, ramipril, an Angiotensin II receptor antagonists, valsartan, candesartan cilextil, and losartan potassium.

18. (Previously Presented) A chronotherapy tablet according to claim 17 wherein the first layer comprises a therapeutically effective amount of diltiazem, the third layer comprises a therapeutically effective amount of diltiazem, and the fifth layer comprises a therapeutically effective amount of diltiazem.

19. (Previously Presented) A chronotherapy tablet according to claim 18 wherein the first layer comprises between about 25 mg-100 mg diltiazem wherein said diltiazem within the first layer is released within about 15 to about 25 minutes of oral administration, and the third layer comprises between about 50 mg-150 mg diltiazem wherein said diltiazem within the third layer is substantially completely releasable within about 15 to about 25 minutes of substantially complete dissolution of the second layer; and, the fifth layer comprises between about 80 mg-200 mg diltiazem wherein said diltiazem within the fifth layer is substantially completely releasable within about 15 to about 25 minutes of substantially complete dissolution of the fourth layer.

20. (Original) A chronotherapy tablet according to claim 19 wherein the first layer comprises about 60 mg diltiazem, the third layer comprises about 180 mg diltiazem, and the fifth layer comprises about 120 mg diltiazem.

21. (Previously Presented) A chronotherapy tablet according to claim 2 wherein a first layer comprises a therapeutically effective amount of a drug, a second layer adjacent to the first layer is a delay layer, a third layer adjacent to the second layer comprises a therapeutically effective amount of a drug, and wherein a therapeutically effective amount of a drug in the first layer is released within about 15 minutes of oral administration of the tablet, and the second layer provides for substantially complete dissolution of the layer to require between about 5 to about 9 hours during dissolution of the core under physiological conditions, and a therapeutically effective amount of a drug in the third layer is substantially completely releasable within about 15 minutes of substantially complete dissolution of the second layer; and, wherein the drug is selected from the group consisting essentially of a beta-2-adrenergic agonist, salbutamol sulphate, terbutaline sulfate, a Systemic Xanthine, aminophyllin, and theophylline.

22. (Original) A chronotherapy tablet according to claim 21 wherein the first layer comprises a therapeutically effective amount of salbutamol, and the third layer comprises a therapeutically effective amount of salbutamol.

23. (Original) A chronotherapy tablet according to claim 22 wherein the first layer comprises between about 2 mg to about 4 mg salbutamol sulphate, and the third layer comprises between about 2 mg to about 4 mg salbutamol sulphate.

24. (Currently Amended) A method of treatment [[and/or prevention]] of a chronobiological

10/697,473

condition comprising orally administering a chronotherapy tablet comprising a [[cylindrical]] cylindrical core having a longitudinal axis, a first end and a second end, the core being comprised of at least two superposed layers of different compositions wherein an interface between each layer is substantially perpendicular to the longitudinal axis of the core and wherein at least one of the layers is a pharmacologically active composition; a coating which envelops the core, except for; at least one exposed release face of the core at at least one end of the core, wherein at least one exposed release face is substantially perpendicular to the longitudinal axis of the core; and, whereas upon oral administration the chronotherapy tablet effects the amelioration of at least one chronobiological condition within 24 hours.

25. (Currently Amended) A method according to claim 24 of treatment [[and/or prevention]] of a chronobiological condition selected from the group consisting essentially of asthma, arthritis, gastrointestinal disorder, cardiovascular disease, and cancer.

26. (Currently Amended) A method according to claim 25 of treatment [[and/or prevention]] of a chronobiological condition of arthritis comprising orally administering a chronotherapy tablet comprising at least two layers of different pharmaceutical compositions and wherein a first layer is a delay layer, a second layer adjacent to the first layer which second layer comprises a therapeutically effective amount of a drug, and a third layer adjacent to the second layer which third layer comprises a therapeutically effective amount of a drug, and wherein the delay layer provides for substantially complete dissolution of the delay layer between about 5 to about 9 hours after oral administration; and, the drug is selected from the group consisting essentially of a nonsteroidal anti-inflammatory agent, acetylsalicylic acid, sodium or potassium diclofenac, etodolac, indomethacin, ketorolac tromethamine, sulindac, tolmetin sodium, cyclooxygenase-2 inhibitor, celecoxib, rofecoxib, a fenamate, mefenamic acid, floctafenine, an oxicam, meloxicam, piroxicam, piroxicam cyclodextrin, tenoxicam, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium, oxaprozin, and diflunisal.

27. (Currently Amended) A method according to claim 25 of treatment [[and/or prevention]] of a chronobiological condition of cardiovascular disease comprising orally administering a chronotherapy tablet comprising a first layer which comprises a therapeutically effective amount of a drug, a second layer adjacent to the first layer which second layer is a delay layer, a third layer adjacent to the second layer which third layer comprises a therapeutically effective amount of a drug, a fourth layer adjacent to the third layer which fourth layer is a delay layer, a fifth layer adjacent to the fourth layer which fifth layer comprises a therapeutically effective amount of a drug, wherein the second and fourth delay layers each provide for substantially complete dissolution of the delay layer to require between about 5 to about 9 hours, each, during dissolution of the core under physiological conditions; and, the drug is selected from the group consisting essentially of an alpha-adrenergic blocking agent, doxazosine mesylate, prazosin hydrochloride, terazosine hydrochloride hydrate, an Alpha & Beta-adrenergic blocking agent, labetalol hydrochloride, a Beta-adrenergic blocking agent, a selective non ISA, atenolol, bisoprolol, esmolol hydrochloride, metoprolol hydrate, a Beta adrenergic blocking agent, a non-selective ISA, oxprinolol hydrochloride, pindolol, a Beta-adrenergic blocking agent, a non-selective non-ISA, nadolol, propanolol hydrochloride, timolol maleate, a centrally acting antiadrenergic agent, clonidine hydrochloride, methyldopa, a Calcium Channel Blocker, amlodipine besylate, diltiazem hydrochloride, felodipine, nifedipine, verapamil Hydrochloride, a Vasolidator, diazoxide, epoprostenol sodium, hydralazine hydrochloride, minoxidil,

10/697,473

nitroglycerine, a Potassium sparing agent, amiloride hydrochloride, spironolactone, triamterene, an Angiotensin converting enzyme inhibitor, benazipril hydrochloride, captopril, enalapril maleate, lisinopril, ramipril, an Angiotensin II receptor antagonists, valsartan, candesartan cilextil, and losartan potassium.

28. (Currently Amended) A method according to claim 25 of treatment [[and/or prevention]] of a chronobiological condition of asthma comprising orally administering a chronotherapy tablet comprising a first layer which comprises a therapeutically effective amount of a drug, a second layer adjacent to the first layer which is a delay layer, a third layer adjacent to the second layer which comprises a therapeutically effective amount of a drug, and wherein a therapeutically effective amount of a drug in the first layer is substantially completely releasable within about 15 minutes of oral administration of the tablet, and the second layer provides for substantially complete dissolution of the layer to require between about 5 to about 9 hours during dissolution of the core under physiological conditions, and a therapeutically effective amount of a drug in the third layer is substantially completely releasable within about 15 minutes of substantially complete dissolution of the second layer; and, wherein the drug is selected from the group consisting essentially of a beta-2-adrenergic agonist, salbutamol sulphate, terbutaline sulfate, a Systemic Xanthine, aminophyllin, and theophylline.